REMARKS

Claims 1, 6-11, 14-16, 18, 20, and 25-38 are pending in the application. No amendments have been made by the present response.

35 U.S.C. §102(b) (Anticipation)

At page 2 of the Office Action, claims 1, 9, 10, 11, 18, 20, and 28-38 were finally rejected as anticipated by Mastrangelo et al. (2000) Biotech. Bioeng. 67:544-54 ("Mastrangelo").

Independent claim 1 is directed to a stable cell line comprising a Chinese Hamster Ovary (CHO) cell comprising an increased amount of Bcl-x_L protein, wherein the cell comprises a first expression vector encoding a secreted protein, and wherein the cell produces an increased amount of the secreted protein as compared to a cell that does not comprise an increased amount of the Bcl-x_L protein. Independent claim 18 is directed to a method of producing a polypeptide in a stable cell line comprising a CHO cell comprising an increased amount of Bcl-x_L protein.

As detailed in the response to the previous Office Action, Mastrangelo describes the ability of Bcl-2 and Bcl-x_L to limit apoptosis upon infection of cells with alphavirus vectors. Cell lines infected with alphavirus vectors undergo apoptosis, and Mastrangelo demonstrated that expression of Bcl-2 or Bcl-x_L in those cells delays the onset of cell death resulting from use of the viral expressions systems. The expression system described by Mastrangelo is a transient one, with variations observed over time both in percentages of cell viability as well as secreted protein levels. In contrast, the cell line of claim 1 (as well as the cell line used in the method of claim 18) is a stable cell line.

The present Office Action asserted that the arguments above were "unpersuasive because Mastrangelo et al., teaches on page 556, right column under the heading 'Cell Cultures' Bcl-Xl over-expressing CHO cells are stable cell line cells."

Applicants respectfully traverse the rejection in view of the following remarks.

As an initial matter, applicants note Mastrangelo does not contain a page 556 (Mastrangelo begins on page 544 and ends on page 554, as noted at page 2 of the Office Action). It is applicants' understanding that the Examiner intended to refer to the heading entitled

"Creation of Stable Transfectants" under the "Materials and Methods" section at page 545 of Mastrangelo. Mastrangelo's use of the term "stable transfectant" in the "Materials and Methods" section and elsewhere in the publication refers to CHO cells stably transfected with a vector encoding Bcl-x_L. It is these stable transfectants that were used by Mastrangelo for subsequent viral infection. Mastrangelo's CHO- Bcl-x_L "stable transfectants" (i.e., before viral infection) do not contain an expression vector encoding a secreted protein, as is required by claim 1. As a result Mastrangelo's CHO- Bcl-x_L "stable transfectants" do not anticipate the claim.

Mastrangelo's susbsequent viral infection of the CHO- Bcl-x_L "stable transfectants" resulted in cells exhibiting clear variations over time in both viability (see Fig. 10) and protein production (see Fig. 12). For example, upon infection of Mastrangelo's CHO- Bcl-x_L cells with the alphavirus vector SFV-IL-12, the cells produced high levels of IL-12 immediately following infection, but secreted only low levels of IL-12 by several days post infection (see daily IL-12 production depicted in Fig. 12a and cumulative IL-12 production depicted in Fig. 12b). Mastrangelo suggested that the replication deficiency of the SFV-IL-12 virus allowed some cells to eventually recover from the viral infection, though the surviving cells produced only low levels of IL-12 (a dramatically reduced amount as compared to the burst of production that occurred in parental CHO cells and CHO- Bcl-x_L cells immediately after infection) (Mastrangelo at page 552). To overcome the problem of short term protein production, Mastrangelo suggested employing a repeated viral infection process as a means to prolong protein production beyond the short burst demonstrated in Fig. 12 (Mastrangelo at page 553). In contrast to the CHO cells used in Mastrangelo's transient viral-based protein production system, the cell line of claim 1 (as well as the cell line used in the method of claim 18) is a stable cell line and produces an increased amount of a recombinant polypeptide as compared to a cell that does not comprise an increased amount of the Bcl-x_L protein. As demonstrated in Figures 9 and 11 of the present application, the claimed cells exhibit enhanced protein production as compared to the parental CHO cells and this enhanced production is maintained throughout the measured duration of the cell culture. Mastrangelo fails to describe such a stable CHO cell line.

In addition to and independent of the remarks above as applied to independent claims 1 and 18, dependent claims 37 and 38 require that the expression vector that is contained within the cell and encodes the polypeptide produced by the cell at increased levels be a plasmid. The SFV-IL-12 vector used by Mastrangelo for IL-12 production is an alphavirus and clearly does not anticipate the plasmid-based system of dependent claims 37 and 38. For this additional reason, the rejection of these dependent claims as anticipated by Mastrangelo cannot stand.

In view of the foregoing comments, applicants respectfully submit that Mastrangelo does not anticipate independent claims 1 or 18 or claims 9, 10, 11, 20, and 28-31 that depend directly or indirectly therefrom. Applicants request that the Examiner withdraw the rejection of the claims.

35 U.S.C. §103(a) (Obviousness)

At page 3 of the Office Action, claims 6, 7, 25, and 26 were finally rejected as unpatentable over Mastrangelo in view of Sinacore et al. (1996) Biotech. Bioeng. 52:518-28 ("Sinacore").

Sinacore was cited as disclosing a strain of CHO cells that is capable of growth in serum-free suspension culture. However, Sinacore provides nothing that supplements the deficiencies of Mastrangelo detailed above with respect to independent claims 1 and 18. Accordingly, once independent claims 1 and 18 are held allowable, dependent claims 6, 7, 25, and 26 should also be in condition for allowance.

At pages 3-4 of the Office Action, claims 14-16 and 32-34 were finally rejected as unpatentable over Mastrangelo in view of Kim et al. (2000) Biotech. Bioeng. 71:184-93 ("Kim").

Kim was cited as disclosing the use of CHO cells to produce an antibody. However, Kim provides nothing that supplements the deficiencies of Mastrangelo detailed above with respect to independent claims 1 and 18. Accordingly, once independent claims 1 and 18 are held allowable, dependent claims 14-16 and 32-34 should also be in condition for allowance.

At page 4 of the Office Action, claims 8 and 27 were finally rejected as unpatentable over Mastrangelo in view of Sinacore (as applied to claims 1, 7, 18, and 26) and further in view of Kim.

Kim was cited as disclosing the use of butyrate in recombinant CHO cell cultures to achieve high level expression of foreign proteins. However, Kim provides nothing that supplements the deficiencies of Mastrangelo detailed above with respect to independent claims 1 and 18. Accordingly, once independent claims 1 and 18 are held allowable, dependent claims 8 and 27 should also be in condition for allowance.

CONCLUSIONS

Applicants respectfully submit that all grounds for rejection have been overcome and that all claims are now in condition for allowance.

Please apply any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 13751-0036US1.

Respectfully submitted,

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/Jack Brennan/
Jack Brennan
Reg. No. 47,443

Fish & Richardson P.C.
601 Lexington Avenue
Floor 52
New York, NY 10022
Telephone: (212) 765-5070
Facsimile: (877) 769-7945